100 000 years ago,[12] at least 100 million years after Gondwana had broken into the continents we know today. *M ulcerans* is thus of relatively recent evolution and the infection it causes does not belong to the Jurassic period.

An explanation is still required as to how the same, or essentially similar, immotile organism may be in distinct, defined, separate loci in three different continents as well as in other apparently isolated locations. Infected insects may represent a local amplification mechanism or a secondary cycle within the aquatic environment, but their infection by itself cannot explain the intercontinental spread of the disease.

Wild ducks (genus *Anas*; figure) have been implicated in occasional, isolated infections in Australian patients. Ducks ingest aquatic plants and insects, and mycobacteria have been shown to survive transit in animal intestines. Ducks are ubiquitous, migrate between continents, and defaecate on water. Instead of drifting on the surface of separating continents over the millennia, *M ulcerans* may well have flown—economy class with stopovers—on its way to establish new foci of infection, flying in the gut of a bird.

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HIV and cytomegalovirus in Thailand

Mahar Ghandi and Rajiv Khanna's recent review of cytomegalovirus infection highlights the important burden of this disease in immunocompromised individuals.[1] In Thailand, where ophthalmological changes due to cytomegalovirus have been observed in a third of HIV-infected patients,[2] management of cytomegalovirus retinitis poses a considerable challenge.

Intervention	Outcome
Intravitreal ganciclovir + HAART (n=5)	Four people retained useful vision One patient became blind and later died
Intravenous ganciclovir for 2 weeks + HAART (n=1)	Patient retained useful vision
HAART only. No cytomegalovirus treatment (n=6)	Two patients retained useful vision One patient was already blind at initiation of HAART and later died Three patients became blind and later died (in two cases, after discontinuing HAART)

HAART=highly active antiretroviral therapy

Table: **Treatment access for patients with cytomegalovirus in three district hospitals in Thailand**

Treatment of opportunistic infections is an integral part of HIV management. Local production of generic HIV medicines[3] in Thailand is making treatment more affordable. For example, 4 years ago treatment of cryptococcal meningitis was out of reach for most because fluconazole cost US$13 a day. Generic production reduced the cost to 30 cents a day and this treatment is now universally available.

Ideally, treatment of cytomegalovirus retinitis requires both intravenous therapy and intravitreal ganciclovir injections, both of which are costly and impractical. Intravitreal injections require referral to an ophthalmologist at provincial level, although in practice few ophthalmologists provide this service. Long-term intravenous therapy is difficult to administer.

Of 228 adults receiving highly active antiretroviral therapy in three district hospitals where we work,[4] cytomegalovirus retinitis was confirmed in 12 severely

immunocompromised patients (table). Those people who received ganciclovir treatment—either intravitreal or intravenous injection, but never both—generally responded well. However, half of the patients were too sick to travel to the referral hospital and therefore received no treatment.

The reality in Thailand is that many cytomegalovirus patients remain untreated. Ganciclovir is a monopoly product and intravenous treatment remains prohibitively expensive, costing US$465 per week. Valganciclovir, which is administered orally, would be highly desirable for use in resource-poor settings, but costs US$840 per week, must be administered for many months, and is not registered in Thailand.

For now, an evaluation of the cost-benefit and feasibility of wider provision of intravitreal ganciclovir injections needs to be undertaken, even though this is considered to be a suboptimal treatment. Future medicines, such as maribavir, are likely to be as irrelevant to Thailand and other developing countries as valganciclovir unless equitable pricing policies are implemented.

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Problem pathogens

Well they all are, I suppose. But what the article on page 345 by David Huang and Herbert DuPont does is review a clinical problem—extra-intestinal complications of typhoid fever—for which there is a paucity of evidence on treatment from randomised trials. This review is the first in an occasional "Problem pathogen" series, which will have as its theme reasonably common infectious conditions whose therapy is uncertain or controversial because of a lack of randomised treatment trials. For coming up with the idea for the series, and for doing much of the leg work of commissioning authors, I thank Victor Yu, University of Pittsburgh, PA, USA. In the words of Professor Yu when he first suggested the series, we hope that these will be decision-facilitating articles for clinicians everywhere.

See **Review** page 345

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